Proper usage of pancreatic enzymes

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With the recognition of the close link between nutritional status and pulmonary function in cystic fibrosis (CF), treatment and prevention of malnutrition have become a major focus in the modern therapeutic approach for patients with CF. Thereby, pancreatic enzyme replacement therapy plays a central role. This article reviews key publications on important aspects of pancreatic enzyme replacement therapy contained in the literature over the last 12 months. New insights into the pathogenesis of exocrine pancreatic disease, efficacy and dosing of pancreatic enzyme preparations, occurrence of fibrosing colonopathy, enzyme replacement in the context of enteral nutrition, and assessment of pancreatic function are addressed. Curr Opin Pulm Med 2002, 8:542–546

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Abbreviations

CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
PI	pancreatic insufficiency
PPI	proton-pump inhibitor
PS	pancreatic sufficiency
VIP	vasoactive intestinal peptide

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Over the last two decades, it has been recognized that nutritional status is closely linked with pulmonary function in cystic fibrosis (CF) and might influence long-term survival and quality of life. Therefore, prevention and treatment of malnutrition have become a major focus in the modern therapeutic approach for patients with CF.

Malnutrition results from an energy deficit derived from an imbalance between energy needs and intake. It is determined by energy losses, energy expenditure, and energy intake. The goal of nutritional care is to establish a positive energy balance, which is achieved by optimizing energy intake and minimizing energy losses. Pancreatic insufficiency (PI) is thereby a main contributing factor to malnutrition, as it leads to maldigestion and malabsorption. Thus, pancreatic enzyme replacement is an important pillar in the therapeutic approach for patients with CF and PI.

This article summarizes recent advances in the literature of the last 12 months and includes publications that advance our understanding of the pathophysiology of pancreatic disease in CF, the assessment of exocrine pancreatic function, as well as some important aspects of pancreatic enzyme replacement therapy.

Assessment of pancreatic function

Accurate assessment of exocrine pancreatic function is a crucial facet of the evaluation and treatment of patients with CF. Pancreatic function tests are used to define pancreatic function in newly diagnosed patients, to monitor patients with pancreatic sufficiency (PS), as well as to monitor efficacy of enzyme replacement therapy.

The function of the exocrine pancreas is difficult to assess because of its anatomic inaccessibility and large reserve capacity. Direct quantification of pancreatic function by pancreozymin-secretin test is certainly the most accurate method, but its complexity, invasive nature, and high costs limit its use in clinical practice. Therefore, interest has been focused on the development of diagnostic tools for the indirect assessment of pancreatic function. The 72-hour fat balance study, which determines fat losses as a percentage of daily fat intake, is still regarded as the "gold" standard test for fat malabsorption in many CF centers. However, it is inconvenient, distasteful to patients, and is prone to sampling errors, leading to the evaluation of other diagnostic tools.

The acid steatocrit has been evaluated as a screening tool for steatorrhea in children with CF and PI, gastrointes-

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tinal disorders, and healthy controls [1]. Median acid steatocrit values discriminated well between groups with steatorrhea and all groups not associated with steatorrhea, but individual values showed a considerable overlap. Some "false positive" results in controls may be explained by the fact that acid steatocrit only measures fat concentration in stool, which does not factor in dietary intake of fat or presence of diarrhea. Thus, the acid steatocrit test has limited value as a simple, nonspecific, screening tool for steatorrhea.

The accuracy of fecal elastase-1 assay as a screening tool for PI was compared with fecal chymotrypsin in patients with CF, healthy controls, and patients with various small intestinal diseases [2]. Fecal elastase-1 is an ELISA test that uses monoclonal antibodies against different specific epitopes of human pancreatic elastase. It is less prone to degradation during intestinal transit than chymotrypsin, is not influenced by exogenous pancreatic enzymes, and shows limited day-to-day variability. Overall, the diagnostic accuracy for fecal elastase-1 was better than for chymotrypsin (92% vs 82%). As a test of PI, fecal elastase-1 was highly specific (100%) when calculated against healthy children, but less specific (86%) in comparison with patients with enteropathies. "False negative" test results may be explained by dilution caused by diarrhea. In general, fecal elastase-1 may be promising as a screening test of pancreatic function. However, its ability to distinguish between PI and PS phenotypes and quantify the degree of pancreatic reserve among patients with CF and PS remains to be defined.

Pancreatic disease in cystic fibrosis and factors that may influence maldigestion and malabsorption

The reserve capacity of the pancreas is very generous. Nutrient maldigestion occurs when the residual capacity for secreting enzymes falls below 1–2% of normal. In approximately half of patients with CF, PI is already present at birth, and, in another 25%, pancreatic failure will develop in the first 6 months of life [3]. The remaining patients will either develop PI later in life or maintain PS long-term. The presence of PI in newborns confirms earlier pathologic studies that pancreatic disease evolves *in utero*. Unlike pulmonary disease, there is close link between pancreatic phenotype (PI or PS) and genotype. Patients carrying two "severe alleles" are almost always PI, whereas those with at least one "mild mutation" are usually PS. The protein product, CF transmembrane conductance regulator (CFTR), functions as a regulated chloride channel at the apical surface of epithelial cells. There is growing evidence that CF-causing mutations alter the function of other channels including bicarbonate secretion in gastrointestinal organs. Bicarbonate secretion appears to be a highly complex process, which is directly or indirectly regulated by various CFTR dependent mechanisms [4,5]. Recent data suggest the presence of "aberrant bicarbonate transport," which may induce pancreatic disease in certain CF-causing mutants despite normal or at least substantial activity of the chloride channel [5]. This emphasizes the importance of bicarbonate transport in the pathogenesis of pancreatic disease in CF. Regardless of the exact mechanisms, CFTR dysfunction impairs chloride and bicarbonate secretion, which, in turn, reduces fluid volume because these anions act as the drawing force for water flow within the pancreatic ducts. Intraluminal acidity and lower volumes lead to precipitation of the protein-rich secretions, causing plugging, obstruction, and progressive damage to the pancreas. Evidence for these disease mechanisms is derived from the CF mouse model [6•] as well as from pancreatic functions studies in patients with CF, showing low flow pancreatic secretions with high protein concentrations. Because CFTR is also expressed in the epithelia of the intestine, it seems likely that decreased bicarbonate secretions across duodenal epithelia contribute to the more acidic intraluminal milieu in patients with CF.

These data suggest that nutrient malassimilation in CF is not only caused by maldigestion from deficiency of pancreatic enzymes, but also is confounded by other factors within the small intestine, including bicarbonate deficiency, abnormalities of mucosal transport, or bile salt deficiency. These factors have important therapeutic implications. It is common knowledge that pancreatic enzyme activity and nutrient absorption are impaired by a low intraluminal pH, highlighting the importance of the "right pH milieu." This raises the question whether suppression of gastric acid secretion is beneficial in the treatment of patients with CF by reducing the acid load delivered to the small intestine. Indeed, recent data provide evidence that proton-pump inhibitors (PPIs) can improve fat malabsorption in subgroups of pancreatic insufficient patients with CF with incomplete response to pancreatic enzyme replacement alone [7].

A recent observation in a CF mouse model led to the interesting hypothesis that increased acidity in the duodenum might enhance secretion of digestive enzymes into pancreatic ducts, thereby causing further intraluminal plugging and damage of pancreatic tissue [6•]. This hypothesis is supported by the observation of significantly lower duodenal pH in the CF mouse, elevated intestinal mRNA levels of secretin, and vasoactive intestinal peptide (VIP), as well as elevated pancreatic VIP-mRNA levels and steady-state pancreatic cAMP. This would suggest that acid induced secretin and VIP stimulation enhances exocrine pancreatic enzyme secretion via hormonal signaling to the pancreas. The assumption that hormonal hyperstimulation of the pancreas might lead to further plugging and progressive damage to the pancreas is only speculative at present. In fact, even the opposite might be true. It could be argued that hormonal hyper-

stimulation might be protective of disease progression in patients with preserved pancreatic function. Nevertheless, these hypotheses raise interesting clinical questions. Would reduction of acid production in the stomach increase the intraluminal pH in the duodenum and thereby relieve the chronic overstimulation of the pancreas and prevent disease progression? Or does the use of pancreatic enzymes in PS patients actually hasten progression of disease through feedback inhibition of secretion? If it could be proven that PPIs were effective in reducing endogenous stimulation to the pancreas and thereby prevent further damage to the pancreas, this therapeutic intervention would have to be implemented shortly after birth, because progression of pancreatic disease might occur early in life. Nevertheless, if it could be proven that use of pancreatic enzymes in PS patients really hastens progression of pancreatic disease, strong arguments would arise against the implementation of pancreatic enzyme replacement therapy without direct evidence of PI, a common practice in many CF centers.

At present, treatment with PPIs can only be considered in situations where there is insufficient control of fat malabsorption to prevent inactivation of pancreatic enzymes and to enhance their digestive activity. Indeed, in recent years, there has been interest in the use of PPIs as adjunctive therapy. Treatment trials with PPIs suggest that they are well tolerated in children with CF [6•,7], but experience with potential long-term side effects is limited. A recent study evaluated children with CF treated with PPI for evidence of vitamin B_{12} deficiency caused by the impaired release of vitamin B_{12} in an alkaline environment [8]. The data showed normal or even elevated levels of vitamin B_{12} and normal levels of homocysteine in children with CF.

Pancreatic enzyme preparations and their efficacy

A wide variety of commercial pancreatic enzyme preparations are available, ranging from conventional products containing pancrelipase powder to various enteric-coated products. Enteric-coated preparations are most frequently used in patients with CF. Most products are acid-resistant, coated microencapsuled enzymes, but products vary considerably in terms of the size of the microcapsules, biochemical coating, and biophysical dissolution properties. Theoretically, variably sized microspheres have an advantage, because they are supposed to distribute more evenly in chyme throughout gastric emptying. However, this theoretical advantage has never been carefully evaluated. The dissolution properties of the pH sensitive coating also depend on the nature of the polymer and the thickness of the protective coating. *In vitro* studies show that the coating of most preparations dissolves over a variable period of time at a pH exceeding 5.5–6.0.

Despite attempts to improve preparations, exogenous pancreatic enzymes have variable efficacy and fail to completely correct maldigestion in most patients with CF and PI for poorly understood reasons. Digestion and absorption is a complex process. Timing is critical. In health, simultaneous secretion of endogenous enzymes and bile with delivery of nutrients to the duodenum is important in initiating intraluminal digestion within the proximal intestine. Compared with endogenous pancreatic enzyme activities in individuals with normal pancreatic function, the release of exogenous pancreatic enzymes in CF may be delayed [9••]. Preliminary results of intubation studies in three patients with CF demonstrated very low enzyme activities in the proximal intestines, highest activities were measured in the jejunum and the ileum. This observation is consistent with previous observations in patients with chronic pancreatitis after the ingestion of enteric-coated preparations. This stands in contrast with observations in healthy individuals, in whom the highest concentration of secreted endogenous enzymes was measured in the duodenum with a considerably fall in enzyme activity as a result of autolysis (esp lipase) with distal transit through the small intestine. Low intraluminal pH did not fully account for the delayed release of exogenous enzymes in the studied patients. Delayed release of enzymes may contribute to intraluminal maldigestion, as it results in a mismatch between intestinal delivery of enzymes, bile acids, and ingested nutrients [9••], and the shortened transit time for assimilation may explain malabsorption.

Additional factors might contribute to the ineffective response to pancreatic enzyme replacement therapy in patients with CF and PI. Poor compliance with enzyme replacement therapy is an important consideration, especially during adolescence and even adulthood. A recent survey demonstrates that body image may significantly affect adherence to nutritional treatments and pancreatic enzyme replacement therapy [10•]. Individual weight perception appeared to be the strongest predictor to adherence or nonadherence. As is the case in the general population, young women with CF tended to overestimate their body weight in comparison with their actual body weight, whereas the opposite was true for men. Despite several biases in the study design (survey by mail-in questionnaires, low response rate, self-reported weights, and incomplete data regarding current pancreatic enzyme replacement), it seems likely that young women with CF are at greater risk than men of disordered body image and disordered eating behavior. From this study, it could not be determined if there was also poor compliance with pancreatic enzyme replacement therapy. Adherence to nutritional treatments and pancreatic enzyme replacement seem to be two important contributing factors in unexplained malnutrition especially in young women with CF.

Dosing of pancreatic enzymes

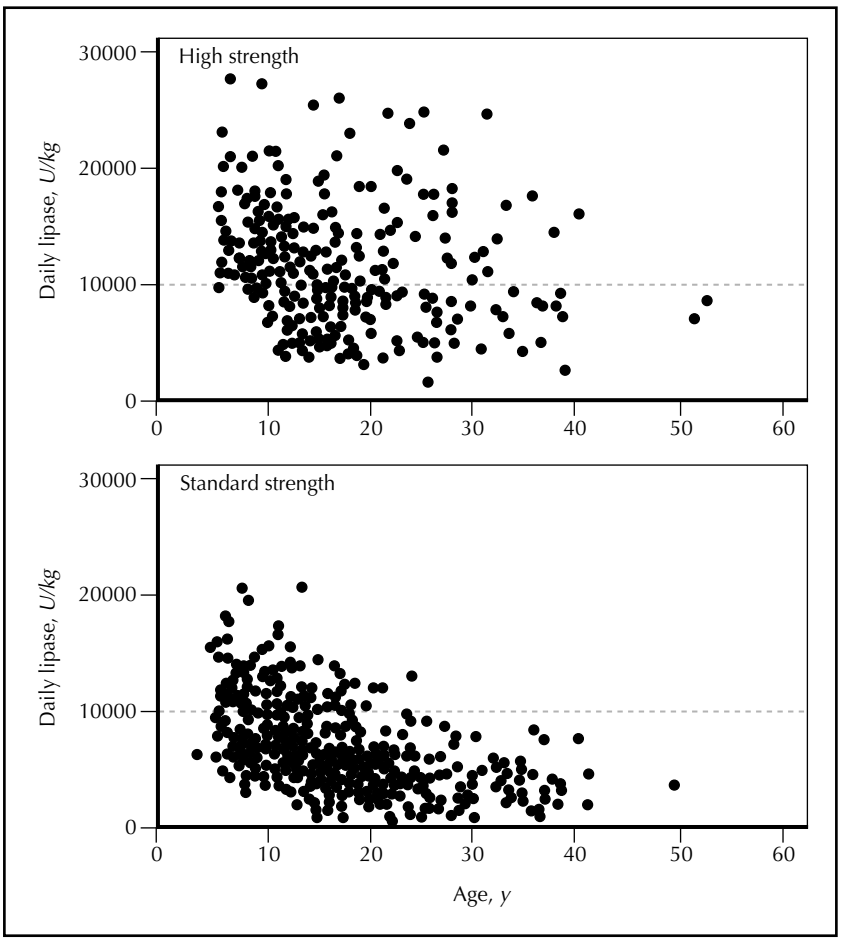
Pancreatic enzyme replacement has long been considered as a safe, well-tolerated treatment for PI in CF. However, in 1994, fibrosing colonopathy was recognized as an iatrogenic complication, and its strong association with high doses of pancreatic enzymes (often in excess of 50,000 U lipase/kg) has led to the re-evaluation of this assumption. Current guidelines from a variety of National Consensus Committees recommend pancreatic enzyme replacement with approximately 1800 U lipase/g fat or 1000–3000 U lipase/kg body weight/meal with an upper limit dose of 10,000 U lipase/kg body weight/d. Some important data regarding the actual use of replacement enzymes have been reported from the United Kingdom [11••]. Audit of the initial validated returns in patients attending CF centers in the United Kingdom (1999–2000) revealed that patients receiving standard strength (10,000 U lipase per capsule) or high-strength (25,000 IU per capsule) pancreatic enzyme formulations commonly exceeded the mentioned current guidelines (Fig. 1). The use of high-strength preparations carried a greater risk of "overdosing," because approximately two-thirds of patients using these preparations exceeded the dosing guidelines, compared with one-third of patients on standard strengths brands. This observation is a concern especially for younger children who appear to carry greater risk of developing fibrosing colonopathy.

Fibrosing colonopathy

Although several countries have implemented strict dosing guidelines for pancreatic enzyme replacement since 1995, further cases of fibrosing colonopathy have been reported in the United States and the United Kingdom. Between 1995 and 1999, 35 new cases of fibrosing colonopathy were reported by CF centers in the United States, and four additional cases were identified in the United Kingdom [12,13]. Thirteen of 35 cases from the United States with histological-confirmed diagnosis were retrospectively analyzed. All patients were children who had received enzyme doses exceeding 2500 U lipase/kg body weight/meal for a mean period of 80.7 months before the diagnosis of fibrosing colonopathy was established. Six of 13 children continued to take high doses for a mean period of 2 years after dosing guidelines were first published [13]. These data give further evidence that "enzyme overdosing" still occurs and also emphasize the need for close monitoring of enzyme doses in all patients with CF.

Figure 1. Replacement enzyme use for high-strength and standard-strength pancreatic enzyme formulations

Dotted line represents Committee on Safety of Medicine's limits. Published with permission [11••].



It has been proposed that specific biochemical coatings of enzyme preparations are associated with fibrosing colonopathy. Bakowski *et al.* [12] argued that the lower prevalence of fibrosing colonopathy in the United Kingdom compared with the United States could actually be attributed to the less frequent use of preparations with coatings containing methacrylic acid copolymer in the United Kingdom. These data have been published only as abstracts, and potential biases are evident. Based on current validated data, no conclusions can be made regarding the safety profile of specific coatings contained in the different high-strength preparations.

Enteral nutrition and pancreatic enzyme replacement

Supplemental enteral tube feeding is a widely used method of improving the nutritional status of underweight patients with CF. Even though many trials provide nutritional benefit evidence, the effect of supplemental feeding on quality of life and long-term survival has not been adequately defined [14]. A recent Cochrane Review comments on the lack of randomized controlled trials, but, in reality, this cannot be achieved because randomization cannot be justified ethically. Data is lacking concerning appropriate dosing and timing of pancreatic enzymes with the different nutritional supplements. Some authors use a single dose of enzymes before beginning the nocturnal enteral infusion with the commonly used intact nutrient formulations, whereas others recommend partially predigested formulations without enzyme supplementation. The efficacy of the different supplements has not been assessed, and no firm conclusions can be drawn regarding the appropriate methods of administering pancreatic enzyme supplements. A recent survey of CF centers in the Netherlands and Belgium revealed various approaches [15]. Enzyme replacement was administered with nocturnal enteral infusions before feeds, before and during feeds, and also before and after feeds, either orally or by tube. Practices differed within the same center and among different care providers. This survey underlines the need for further research in this area to achieve an evidence-based consensus on the optimal method of providing nutrient supplements to patients with CF.

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